Tyrosine Hydroxylase Phosphorylation

Subjects: Biochemistry & Molecular Biology

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Tyrosine hydroxylase (TH) is the rate-limiting enzyme of dopamine biosynthesis. The phosphorylation of TH is strictly regulated.

tyrosine hydroxylase | phosphorylation | dephosphorylation | cAMP-dependent protein kinase | protein phosphatase 2A | dopamine | ubiquitin-proteasome system

1.Introduction

TH is activated by phosphorylation by a cAMP-dependent protein kinase and deactivated by dephosphorylation by protein phosphatase 2A. The dysregulation of TH phosphorylation leads to its aggregation or degradation by the ubiquitin-proteasome system, presumably associated with the etiology of Parkinson's disease and dopa-responsive dystonia.

2.Physiology

Tyrosine hydroxylase (TH) is a rate-limiting enzyme for dopamine biosynthesis [1] and is selectively expressed in monoaminergic neurons in the central nervous system. In humans, TH protein has four isoforms with different molecular weight, which are derived from the same gene through alternative splicing of mRNA [2][3]. This protein also has two isoforms in monkeys and only a single isoform in all nonprimate mammals [4][5]. The catalytic domain of TH is located within the C-terminal area, whereas the region that controls enzyme activity (the regulatory domain) is located at the N-terminal end [6]. Four phosphorylation sites, namely Ser8, Ser19, Ser31, and Ser40, have been identified in the N-terminal region of TH [7], whereas the catalytic domain is in 188–456 amino acid residue [8]. TH is a homotetramer consisting of four subunits, and the C-terminal domain forms this homotetramer structure [9]. The phosphorylation of TH is strictly regulated [10][11]. The dysregulation leads to its aggregation [12][13] or degradation by the ubiquitin-proteasome system [14][15].

Two mechanisms can modulate the activity of TH: one is a medium- to long-term regulation of gene expression, such as enzyme stability, transcriptional regulation, RNA stability, alternative RNA splicing, and translational regulation. The regulation of TH is well known; its expression level depends on transcription driven by cyclic adenosine monophosphate (cAMP)-dependent responsive element (in promoter) [16] in a manner dependent on activator protein 1 (AP-1) [17][18], serum-responsive factor (SRF) [19], and nuclear receptor related-1 (Nurr1) [20]. The other is a short-term regulation of enzyme activity, such as feedback inhibition, allosteric regulation, and

phosphorylation [16][10][11]. Many factors strictly regulate the activity of TH to control dopamine biosynthesis. Upon depolarization, cyclic AMP-dependent protein kinase (PKA) and calcium-calmodulin-dependent protein kinase II (CaMKII) are activated [21][22][23]. PKA phosphorylates TH at Ser40 and CaMKII phosphorylates TH at Ser19 [24][25]. Phosphorylation of Ser19 increases Ser40 phosphorylation, indicating that the phosphorylation of Ser19 can potentiate the phosphorylation of Ser40 and subsequent activation of TH [26]. Other stress-related protein kinases can also phosphorylate TH at Ser40 [10][11]. Phosphorylation at Ser40 leads to the liberation of dopamine from the active site of TH and changes the conformation to the high specific activity form [27]. Cytosolic free dopamine can bind to the active site of TH and deactivate the enzyme to suppress dopamine overproduction [28][29]. It has been reported that the phosphorylated form of TH is highly labile, whereas the dopamine-bound form is stable [30]. TH phosphorylated at Ser40 (pSer40-TH) is dephosphorylated by a protein phosphatase, such as protein phosphatase 2A (PP2A), because inhibition of PP2A with okadaic acid or microcystin induces an increase in pSer40-TH level [31][32][33]. Ser31 phosphorylation is mediated by extracellular signal-regulated kinase 1 (ERK1) and ERK2 [5][34], and its dephosphorylation is mediated by PP2A [33]. Because ERK signals are usually activated as part of the mitogen-activated protein kinase (MAPK) cascade for cell survival, dephosphorylation of TH phosphorylated at Ser31 (pSer31-TH) is very rare in living cells. Phosphorylation of TH at Ser8 has been shown in cultured rat pheochromocytoma PC12 cells and permeabilized bovine chromaffin cells after treatment with okadaic acid [24][33]. In contrast, no significant phenomena have been reported in cultured dopaminergic neurons and *in vivo*. These data suggest that TH regulation by Ser8 phosphorylation is not critical in the central nervous system.

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